Amendments to the Specification

Please add the following paragraphs after the paragraph ending on page 45, line 28:

-- **Carrier Linkages for Various Functional Groups**

a. Alcohols and Carboxylic Acids. There are several reasons why the most common prodrug form for drugs containing alcohol or carboxylic acid functional groups is an ester. First, esterases are ubiquitous, so metabolic regeneration of the drug is a facile process. Also, it is possible to prepare ester derivatives with virtually any degree of hydrophilicity or lipophilicity. Finally, a variety of stabilities of esters can be obtained by appropriate manipulation of electronic and steric factors. Therefore, a multitude of ester prodrugs can be prepared to accomodate a wide variety of problems that require the prodrug approach.

Alcohol-containing drugs can be acylated with aliphatic or aromatic carboxylic acids to decrease water solubility (increase lipophilicity) or with carboxylic acids containing amino or additional carboxylate groups to increase water solubility. Conversion to phosphate or sulfate esters also increases water solubility. By using these approaches a wide range of solubilities can be achieved that will affect the absorption and distribution properties of the drug. These derivatives also can have an important effect on the dosage form, that is, whether used in a tablet form or in aqueous solution. One problem with the use of this prodrug approach is that in some cases the esters are not very good substrates for the endogenous esterases, sulfatases, or phosphatases, and they may not be hydrolized at a rapid enough rate. When that occurs, however, a different ester can be tried. Another approach to accelerate the hydrolysis rate could be to attach electron-withdrawing groups (if a base

hydrolysis mechanism is relevant) or electron-donating groups (if an acid hydrolysis mechanism is important) to the carboxylate side of the ester. Succinate esters can be used to accelerate the rate of hydrolysis by intramolecular catalysis. If the ester is too reactive, substituents can be appended that cause steric hindrance to hydrolysis. Alcohol-containing drugs also can be converted to the corresponding acetals or ketals for rapid hydrolysis in the acidic medium of the gastrointestinal tract.

Carboxylic acid-containing drugs also can be esterified; the reactivity of the derivatized drug can be adjusted by the appropriate structural manipulations. If a slower rate of ester hydrolysis is desired, long-chain aliphatic or sterically hindered esters can be used. If hydrolysis is too slow, addition of electron-withdrawing groups on the alcohol part of the ester can increase the rate. The pKa of a carboxylic acid can be raised by conversion to a choline ester or an amino ester.

b. Amines. N-Acylation of amines to give amide prodrugs is not commonly used, in general, because of the stability of amides toward metabolic hydrolysis. Activated amides, generally of low basicity amines, or amides of amino acids are more susceptible to enzymatic cleavage. Although carbamates in general are too stable, phenyl carbamates (RNHCO2Ph) are rapidly cleaved by plasma enzymes, and, therefore, they can be used as prodrugs.

The pKa values of amines can be lowered by approximately 3 units by conversion to their *N-Mannich bases*. This lowers the basicity of the amine so that at physiological Ph few of the prodrug molecules are protonated, thereby increasing its lipophilicity. For example, the partition coefficient between octanol and phosphate buffer, pH 7.4, for the N-Mannich base derived from benzamide and the decongestant phenylpropanolamine is almot 100

times greater than that for the parent amine. However, the rate of hydrolysis of N-Mannich bases depends on the amide carrier group; salicylamide and succinimide are more susceptible to hydrolysis than is benzamide.

Another approach for lowering the pKa values of amines and, thereby, making them more lipophilic, is to convert them to imines (*Schiff bases*); however, imines often are to labile in aqueous solution. The anticonvulsant agent progabide (8.3) is a prodrug from of γ-aminobutyric acid, an important inhibitory neurotransmitter. The lipophilicity of 8.3 allows the compound to cross the blood-brain barrier; once inside the brain it is hydrolized to γ-aminobutyric acid.

c. Carbonyl Compounds. The most important prodrug forms of aldehydes and ketones are Schiff bases, oximes, acetals (ketals), enol esters, oxazolidines, and thiazolidines (Table 8.3). A more complete review of bioreversible derivatives of the functional groups was written by Bundgaard.--